A matching-adjusted indirect comparison (MAIC) of zanubrutinib vs venetoclax + ibrutinib in treatment-naive chronic lymphocytic leukemia (CLL)

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ABSTRACT

Introduction: Zanubrutinib is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor approved for the treatment of CLL. The phase 3 SEQUOIA trial (NCT03336333) evaluated zanubrutinib in treatment-naive (TN) patients without del(17p) mutations (arm A), in comparison with bendamustine + rituximab in the same population (arm B), and as monotherapy in patients with del(17p) mutations (arm C). Venetoclax combined with the first-generation BTK inhibitor ibrutinib (V+I), has regulatory approval outside of the United States in TN CLL. This regimen has been evaluated in two key trials: GLOW (NCT03462719), which enrolled older and/or comorbid patients without del(17p)/*TP53* mutations, and CAPTIVATE (NCT02910583), which included younger patients regardless of del(17p)/*TP53* status. This study compared zanubrutinib vs V+I using the latest data cutoff for all included trials through a MAIC.

Methods: A population-adjusted indirect comparison between zanubrutinib and V+I was performed to mitigate potential bias due to differences in study populations. As neither GLOW nor CAPTIVATE could be connected to SEQUOIA through a common control arm, 2 unanchored MAICs were conducted. Individual patient data from arm A and arms A+C of SEQUOIA (median follow-up, 74.4 months) were matched to the V+I arms of GLOW (median follow-up, 67.0 months) and CAPTIVATE (median follow-up, 69.0 months), respectively. Adjustments for age, sex, geographic region, CLL stage, cancer type, cytogenetic mutations, complex karyotype, Eastern Cooperative Oncology Group performance status, bulky disease, time from diagnosis, β2-microglobulin, and creatinine clearance were considered based on data availability and the magnitude of imbalance between populations. Weighted Cox regression was used to estimate hazard ratios (HRs).

Results: For progression-free survival (PFS) in SEQUOIA vs GLOW, both the unadjusted and adjusted comparisons of zanubrutinib (SEQUOIA arm A; n=241) and V+I (GLOW; n=106) indicated a treatment benefit in favor of zanubrutinib, with an unadjusted HR of 0.49 (95% CI, 0.33-0.72; *P*=.0005) and an adjusted HR of 0.57 (95% CI, 0.37-0.87; *P*=.0098); the effective sample size (ESS) for the adjusted zanubrutinib cohort was 152.4. For PFS in SEQUOIA vs CAPTIVATE, the unadjusted comparison of zanubrutinib (arms A+C; n=352) and V+I (CAPTIVATE; n=159) indicated a treatment

benefit in favor of zanubrutinib (HR, 0.64; 95% CI, 0.47-0.88; *P*=.0065). After matching, the adjusted HR remained favorable for zanubrutinib (HR, 0.54; 95% CI, 0.29-1.01; *P*=.0527); however, the result was not statistically significant, likely due to a substantially reduced zanubrutinib sample size (ESS, 50.5), reflecting large differences between the SEQUOIA and CAPTIVATE populations and resulting in limited statistical power. Sensitivity analyses exploring the impact of using different sets of matching factors in the efficacy comparisons showed consistent results.

Conclusions: With the longest available follow-up, zanubrutinib demonstrated a statistically significant PFS benefit over V+I in the GLOW population. In the comparison of CAPTIVATE vs SEQUOIA, a trend favoring zanubrutinib was observed, though statistical significance was not reached due to limited ESS caused by substantial baseline heterogeneity. These findings reinforce the robustness of the efficacy of zanubrutinib in TN patients with CLL and suggest improved outcomes compared with fixed-duration V+I across diverse patient populations. However, as this was an unanchored MAIC, the analysis is subject to limitations, including potential residual confounding and reduced statistical power due to differences in trial populations and designs.